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PREGNANCY, PRUDENCE, AND DIETARY SUPPLEMENTS

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FDA Public Meeting on Pregnancy-Related Statements of Nutritional Support, Including Structure/Function Statements
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Although pregnancy is a "natural state," as the term is used in FDA's final rule on structure/function statements, it is a state to be treated with the utmost respect and caution. This applies to the marketing and use of dietary supplements, as well as to many other products and practices. The Council for Responsible Nutrition (CRN) is a trade association representing approximately 100 manufacturers of dietary supplements and their ingredients.

CRN recognizes the need to assure that all dietary supplements are safe and beneficial, but also recognizes an increased need for prudence when dealing with products intended for use by pregnant or nursing women. In the interest of extreme prudence, CRN members would support an FDA finding that statements relating to morning sickness or edema of pregnancy must meet a rigorous standard of evidence regarding safety as well as benefit. We believe DSHEA provides ample authority for FDA to establish criteria for safety that must be met before products can be offered for use during pregnancy. Criteria could also be established for determining the adequacy of a company's substantiation for any statement of nutritional support pertaining to pregnancy.

BACKGROUND ON THE EXTENT AND IMPORTANCE OF SUPPLEMENT USE BY WOMEN OF CHILDBEARING AGE

In discussing dietary supplements and pregnancy, it is important to recognize the extent and importance of dietary supplement use -- especially vitamin and mineral supplement use -- by women of childbearing age.

According to NHANES III, dietary supplements are used by almost 30% of teenage girls and by over 40% of women between the ages of 20 and 39 in the U.S. Among women

20-39, 65% of those who use a supplement use only one product, and 83% of the time that one product is a multivitamin, with or without minerals. Other commonly used nutritional products include vitamin C, vitamin E, and calcium. More detail on usage of supplements by these age groups of women is provided in Attachment A.

Prenatal vitamin and mineral supplements are almost universally recommended by physicians, and are used by more than 80% of pregnant women. Prescription prenatal products are often specifically recommended by physicians and are usually reimbursable, but dietary supplement prenatal products with similar formulations are also available.

CRN believes it is important to be clear about the benefits of appropriate nutritional supplementation for women who may become pregnant, as well as for women who are already pregnant or nursing. While we recognize the basis of the concerns that led to this public meeting, we are anxious to assure that women do not get the wrong message and turn away from multivitamins, calcium products, and prenatal supplements known to be beneficial. Nutritional supplements such as these may or may or may not bear structure/function statements or health claims. They may simply be labeled for use by all adults or specifically by women, or may be directly intended for pregnant or nursing women. FDA has established Reference Daily Intakes to be used in labeling vitamin and mineral products for use by adults generally, and a separate set of values to be used in labeling products for use by pregnant or nursing women.

Dietary supplements containing calcium or folic acid may also be labeled with an FDA-authorized health claim -- a category of claims that is distinct from statements of nutritional support (structure/function claims). The health claim for calcium and osteoporosis was authorized by FDA in 1993, and the health claim for folic acid and neural tube birth defects was authorized in 1996.

STATEMENTS OF NUTRITIONAL SUPPORT, INCLUDING STRUCTURE/FUNCTION STATEMENTS

In 1994, Congress passed the Dietary Supplement Health and Education Act (DSHEA), which permitted dietary supplements to bear Statements of Nutritional Support, including statements describing the effect of a product on the structure or function of the body. For more than five years, the industry has been making label statements under these provisions, including some statements relating to women's health issues. CRN recently reviewed a database covering 3600 Statements of Nutritional Support, including 200 statements relating to women's health. There was not a single statement relating to morning sickness or edema of pregnancy. There were only a few statements relating to pregnancy in any way, and these involved unsaturated fatty acids including DHA and EPA. There is substantial evidence on the benefits of these omega-3 fatty acids for the mother, the fetus, and the newborn infant. Most of the structure/function statements relating to women's health were focused on PMS or menopause.

In 1998, FDA proposed regulations to better define the permissible scope of structure/function statements for dietary supplements. In the proposal, the agency took a

narrow view of permissible statements about "natural states" such as aging, menopause, and pregnancy. Numerous comments complained that FDA was wrong in considering many symptoms associated with natural states to be disease conditions. In the final rule published January 6, 2000, FDA reversed its position in part by acknowledging that statements could reasonably be made about some natural states, without being disease claims. As examples of these, FDA included statements about morning sickness and leg edema of pregnancy.

Well respected physicians immediately expressed concern to FDA about the potential risk to pregnant women and to unborn babies, if a wide variety of dietary supplements were suddenly to be offered for use in morning sickness or edema of pregnancy. The degree of concern was triggered in part by the tragic history of some pharmaceutical products which were offered for treatment of morning sickness and which were later found to increase the risk of birth defects. FDA issued an advisory to the industry, indicating that the morning sickness and edema statements should not be used, pending a public meeting and further agency consideration of this issue.

CRN is not aware that anyone in the industry had expressed interest in making label statements about these particular conditions, or that any of our member companies are now making label statements about these conditions. We are not aware of any dietary supplement that might potentially be labeled for uses related to edema of pregnancy, but there are a few botanicals that are commonly considered to have uses in morning sickness. Many women are well aware of these potential uses, whether or not the product is labeled with a specific indication for morning sickness. For example, a recent article in the lay press discussed the benefits of raspberry leaf tea and ginger for the relief of morning sickness, and these botanicals are affirmatively recommended for these uses in some herbal pharmacopeias and other professional references.

CONCLUSIONS

CRN and its members have no wish to see inappropriate products offered for use for morning sickness or edema of pregnancy, or for any other use that could be detrimental to pregnant or nursing women or to women who may become pregnant. At the same time, we do not believe it would be reasonable to classify pregnancy as a disease, or to classify such common pregnancy-related conditions as morning sickness as diseases.

The key issue in the present controversy is not in fact related directly to claims, but is rather a concern about the safety of any product specifically marketed for use by pregnant or nursing women. CRN believes, as a matter of policy, it would be preferable to address these safety concerns directly rather than choose the indirect route of prohibiting particular claims.

We believe DSHEA permits FDA to establish a rigorous requirement for evidence of safety for products bearing pregnancy-related statements, as well as a rigorous requirement for substantiation of any claims.

CRN specifically recommends that FDA should:

- Issue a guidance document setting forth the data that FDA would consider to be necessary to substantiate a label statement about morning sickness or edema of pregnancy (or about other conditions related to pregnancy). DSHEA requires that manufacturers have substantiation for statements of nutritional support. DSHEA did not establish criteria for that substantiation, and FDA has not established any criteria by regulation. The Commission on Dietary Supplement Labels set forth several recommendations regarding the quality and quantity of substantiation that would be appropriate and emphasized that the substantiation should cover safety as well as effectiveness. The Commission recommendations provide a model that FDA could consider incorporating into a guidance document.

- Issue a guidance document setting forth the conditions under which FDA would consider a product bearing a pregnancy-related statement to be adulterated. In such a document, FDA could indicate that a product intended for use in pregnancy would be considered to "present a significant or unreasonable risk" if it is not recognized as safe for use during pregnancy, or if there is not sufficient evidence to support such a finding.

In summary, CRN recognizes the obligation of the industry to provide safe products to the consumer and to substantiate label claims. These obligations take on special significance when they are applied to products intended for use during pregnancy. We believe DSHEA provides ample authority for FDA and the industry deal with product safety and with label substantiation, and we believe that authority can be used to resolve the concerns that have been expressed regarding pregnancy-related products and claims.

ANSWERS TO QUESTIONS POSED BY FDA

1. What are the potential hazards that may be associated with use of dietary supplements for conditions associated with pregnancy, both to the pregnant woman and the fetus? Should these hazards be considered to be different than hazards to other potential users of dietary supplements? If so, why and on what basis under DSHEA?

CRN Response: The hazards associated with any product used in pregnancy include any harm to the pregnant woman or to the developing fetus. In our society, we have historically placed particular emphasis on such hazards and have taken extraordinary measures to avoid the potential for unanticipated harm. DSHEA provides ample authority for addressing this situation. For example, DSHEA requires manufacturers to have substantiation for all statements of nutritional support. FDA could provide guidance regarding the type and degree of substantiation required for pregnancy-related statements. The report of the Commission on Dietary Supplement Labels set forth some considerations which could provide a model. DSHEA also declares a product to be adulterated if it poses a significant or unreasonable risk. FDA could provide guidance

establishing the proposition that a product intended for use in pregnancy will be considered adulterated under DSHEA unless there is appropriate evidence to support the safety of such use. In considering the evidence that would be appropriate to evaluate either safety or efficacy, existing expert or authoritative recommendations should be taken into account. These may include recommendations of bodies such as the Food and Nutrition Board, Commission E, the Public Health Service, the U.S. Pharmacopeia (and possibly other national pharmacopeias), and similar groups that have evaluated particular nutrients or other substances marketed as dietary supplements.

2. Are there certain conditions associated with pregnancy for which structure/function claims should not be permitted? If so, why and on what basis?

CRN Response: Rather than prohibit particular statements or classes of statements, CRN recommends that FDA consider approaching the issue from the point of view of the evidence required to substantiate both safety and efficacy for products offered for pregnancy-related conditions. However, we do not disagree with FDA's conclusion that toxemia of pregnancy should be considered a disease condition.

3. What is the potential for harm that may be associated with the use of dietary supplements during pregnancy for conditions unrelated to pregnancy?

CRN Response: Alcohol and cigarettes are examples of products used for reasons unrelated to pregnancy, but which may have profound negative effects on pregnancy and the health of the fetus. In the dietary supplement arena, vitamin A is the classic example of an essential nutrient that is required for general health and specifically for a healthy pregnancy, but that also poses a risk when used in excessive amounts during pregnancy. CRN has recommended limits on vitamin A levels in dietary supplements, and the state of California has listed vitamin A in excess of 10,000 IU as a teratogen under Prop 65. There are some products which are contraindicated in pregnancy, including some botanicals reviewed by Commission E or covered in the Botanical Safety Handbook published by the American Herbal Products Association. Some stimulant botanical products such as ephedra have been the subject of extensive consideration by FDA and already bear extensive warning statements, including advice that they should not be used by pregnant or nursing women.

4. Are there means to address safety concerns association with dietary supplement use during pregnancy, for example, a requirement to conduct animal studies or collect human safety information?

CRN Response: As indicated above, in response to question 1, we note that DSHEA provides ample authority for FDA to declare a product adulterated on the grounds that it poses a significant or unreasonable risk. We believe this authority could provide the basis for FDA guidance regarding the evidence necessary to establish the safety of products intended for use during pregnancy.

5. Should dietary supplements with a specific recommended use during pregnancy be required to bear specific warnings about use during pregnancy? Should all dietary supplements be required to bear such warnings?

CRN Response: CRN believes it would be inappropriate and counterproductive to have warnings about use during pregnancy on a product actually intended for use during pregnancy. Any such products should be held to a rigorous standard of evidence, both to support safety during pregnancy and to support any claims made for the products.

Where there is a known contraindication against use of a product during pregnancy, as indicated for example in the *Botanical Safety Handbook* published by the American Herbal Products Association, the product should be labeled with a caution against use in pregnancy.

For other dietary supplements, CRN believes the current focus should be on resolving the underlying questions regarding whether certain pregnancy-related claims can be made and regarding the evidence required to substantiate safety and label claims for any pregnancy-related claims that are permitted.

ATTACHMENT A, page 1:

**NHANES III, 1988-1994, WOMEN
OF CHILDBEARING AGE WHO USED SUPPLEMENTS
IN THE MONTH BEFORE THE INTERVIEW
(multivit/min = multivitamin with minerals)**

FEMALES 12-19

Percent who used any supplement:	28%
Percent of supplement users who used only 1 product:	78%
Percent of supplement users who used 2 products:	15%
Percent of supplement users who used 3 or more products:	7%

Of those who used only 1 product:	70% used a multivitamin or multivit/min
	18% used a single vitamin
	7% used a single mineral
	<2% used some other supplement
Of those who used 2 products:	90% used a multivitamin or multivit/min
	55% used a single vitamin
	33% used a single mineral
	10% used some other supplement
Of those who used 3 or more products:	85% used a multivitamin or multivit/min
	95% used a single vitamin
	65% used a single mineral
	28% used some other supplement

ATTACHMENT A, page 2:

NHANES III, 1988-1994, WOMEN OF CHILDBEARING AGE WHO USED SUPPLEMENTS IN THE MONTH BEFORE THE INTERVIEW
(multivit/min = multivitamin with minerals)

FEMALES 20-39

Percent who used any supplement:	42%
Percent of supplement users who used only 1 product:	65%
Percent of supplement users who used 2 products:	21%
Percent of supplement users who used 3 or more products:	14%

Of those who used only 1 product:	83% used a multivitamin or multivit/min
	8% used a single vitamin
	6% used a single mineral
	<1% used some other supplement
Of those who used 2 products:	92% used a multivitamin or multivit/min
	48% used a single vitamin
	31% used a single mineral
	12% used some other supplement
Of those who used 3 or more products:	99% used a multivitamin or multivit/min
	82% used a single vitamin
	50% used a single mineral
	44% used some other supplement